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DOCK1 a new candidate gene in inherited form of mitral valve prolapse

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Mitral valve prolapse (MVP) affects 2-4% of the general population and remains one of the most frequent indications for valvular surgery. So far, the only gene described in MVP, with an X-linked form of inheritance, is *FLNA* but only represents a small part of MVP.

To this respect, we investigated a french MVP pedigree to uncover new molecular insights associated to the disease. We focus on a family of 5 affected patients characterized by a dysmorphic myxomatous phenotype with 2 operated patients.

From 4 MVP patients, we performed a Whole Exome Sequencing screening. From bioinformatics analysis, we focused on rare (MAF<0.1%) functional variants shared by the 4 affected patients. Among 25 variants of interest, 11 were novel. One of them, found in a highly conserved residue (GERP=4.88), in *DOCK1* (c.4646G>A; p. R1549Q) co-segregates in all affected members in the family. *DOCK1* is highly expressed in the mitral valve as evidenced by RNA sequencing experiments using human mitral valve tissue.

DOCK1, encodes an atypical Rac exchange factor, Dock180, which acts as a guanine exchange factors (GEF) for small Rho family G proteins. Interestingly, Sanematsu *et* al. (2010) described a major role of Dock180 during cardiovascular development. Mitral valves of Dock1 depleted mice are thickened and lead to blood retention in left atrium. We currently investigate repercussions of p. R1549Q (located in GEF activity domain of Dock180) on Dock180 activity in the cellular adhesion phenotype (XCELLigence; IF assays) and GEF activity (Pull-Down assays) using a heterologous transfection system. Finally, a cohort of 285 MVP affected patients is screened to evaluate the prevalence of *DOCK1* in the disease. This study reports a familial approach, coupled to an exome sequencing strategy which identifies a novel *DOCK1* missense mutation associated with MVP phenotype. In vivo previous studies and cellular mechanisms learning will allow us to better understand mechanisms involved in the MVP pathogenesis.